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Cardiovascular Risk with Gender-Affirming Hormone Therapy

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Historical Perspective

Gender incongruence refers to a persistent mismatch between an individual's experienced gender and the sex assigned at birth. While modern terminology is recent, descriptions of gender variance date back to antiquity, including writings attributed to Hippocrates.

By the 7th century, Paul of Aegina, in his *Medical Compendium*, described surgical procedures aimed at modifying sex characteristics. While these early interventions were not grounded in a modern understanding of gender identity, they reflect attempts to address distress related to discordance between physical characteristics and lived experience. For much of history, surgical intervention—most commonly orchiectomy—remained the primary medical approach.[1]

A more structured medical understanding began to emerge in the early 20th century, including the establishment of early centres dedicated to the study and care of gender-diverse individuals.

In modern practice, access to gender-affirming hormone therapy (GAHT) and surgical interventions has improved. However, there remains a relative paucity of high-quality clinical research to guide management. Randomized controlled trials are lacking, and current recommendations are largely based on retrospective observational studies and extrapolation from cisgender populations. This limited evidence base makes it challenging to balance treatment goals with risk mitigation—particularly with respect to cardiovascular disease. This brief review aims to summarize the current evidence and provide a practical framework for clinicians.

GAHT and Cardiovascular Disease and Mortality

Historically, concerns have been raised regarding the potential adverse cardiovascular effects of exogenous sex hormone therapy. Evidence from cisgender populations, however, suggests a more nuanced relationship. In appropriately selected individuals, hormone

therapy does not appear to confer uniform cardiovascular harm and may, in some contexts, be cardiometabolically neutral or beneficial.[2-5]

In gender-diverse populations, uncertainties remain, as the effects of GAHT occur in a different physiologic context. At present, there are no randomized controlled trials and limited prospective data evaluating the impact of GAHT on hard cardiovascular outcomes such as myocardial infarction, stroke, or cardiovascular mortality. Only a small number of observational studies have examined these outcomes directly.

One of the largest available datasets comes from a Dutch cohort study evaluating approximately 3,000 individuals assigned male at birth (AMAB) receiving feminizing hormone therapy and over 1,500 individuals assigned female at birth (AFAB) receiving masculinizing therapy between 1972 and 2018. In both cohorts, overall mortality was higher compared to age-matched cisgender controls. Among AMAB individuals, excess mortality was primarily driven by cardiovascular disease, lung cancer, HIV-related illness, and suicide. In the AFAB cohort, higher mortality from non-natural causes was observed, although no single predominant etiology was identified. These trends were consistent across the five decades of follow-up.[6]

Overall, data are limited and do not demonstrate a clear association between GAHT and major cardiovascular outcomes, including atherosclerotic cardiovascular disease, myocardial infarction, coronary intervention, cerebrovascular disease, and peripheral arterial disease.[7] One retrospective study did report an association between the use of GAHT and rates of myocardial infarction; however, traditional cardiovascular risk factors such as diabetes and hypertension were substantially stronger predictors of risk.[8] The most consistent signal across the literature is an increased risk of venous thromboembolism (VTE) among AMAB individuals receiving estrogen therapy. This association is biologically plausible and mirrors the known prothrombotic effects of systemic estrogen observed in cisgender women.

GAHT and Cardiometabolic Risk Factors

Sex hormones are known to influence lipid metabolism, and similar patterns are observed in both cisgender and transgender populations. Testosterone therapy is associated with a more atherogenic lipid profile, characterized by increases in low-density lipoprotein (LDL) cholesterol and reductions in high density lipoprotein (HDL) cholesterol, in both cisgender men and transgender individuals (**Figure 1**).[9]

Estrogen, in contrast, is associated with increases in triglyceride levels. This effect may be more pronounced in AMAB individuals initiating feminizing hormone therapy, in whom significant elevations in triglycerides can occur, particularly with oral formulations. These effects reflect the underlying hepatic and metabolic pathways through which sex hormones influence lipid metabolism.[10]

Emerging data suggest that GAHT may influence insulin sensitivity and diabetes risk, although findings remain heterogeneous. Testosterone therapy has been associated with increased insulin resistance and a shift toward central adiposity, both of which are established contributors to adverse metabolic risk.[11]

In contrast, estrogen therapy is more commonly associated with overall weight gain and increased adiposity, which may also contribute to worsening insulin sensitivity through a different metabolic pathway (**Figure 2**). As such, both feminizing and masculinizing hormone therapies may be associated with an increased risk of type 2 diabetes, albeit via distinct mechanisms. Observational data from large cohort studies support this signal, although findings are limited by potential confounding and should be interpreted with caution.[11]

Evidence regarding the impact of GAHT on blood pressure is limited and inconsistent. Both feminizing and masculinizing hormone therapies may influence blood pressure through distinct mechanisms, including effects on fluid balance, vascular tone, and body composition; however, no clear or consistent association with hypertension has been established. As such, blood pressure management in individuals receiving GAHT should follow standard approaches based on overall cardiovascular risk rather than being attributed solely to hormone therapy.[12]

The role of progesterone in feminizing GAHT remains unclear. While some patients and clinicians use it with the aim of improving breast development, mood, or sleep, supporting evidence is limited, and data on cardiovascular effects in transgender populations are sparse. Evidence from cisgender populations suggests that risk may vary by formulation, with synthetic progestins having less favourable cardiometabolic and thrombotic profiles compared to micronized progesterone. However, whether these findings

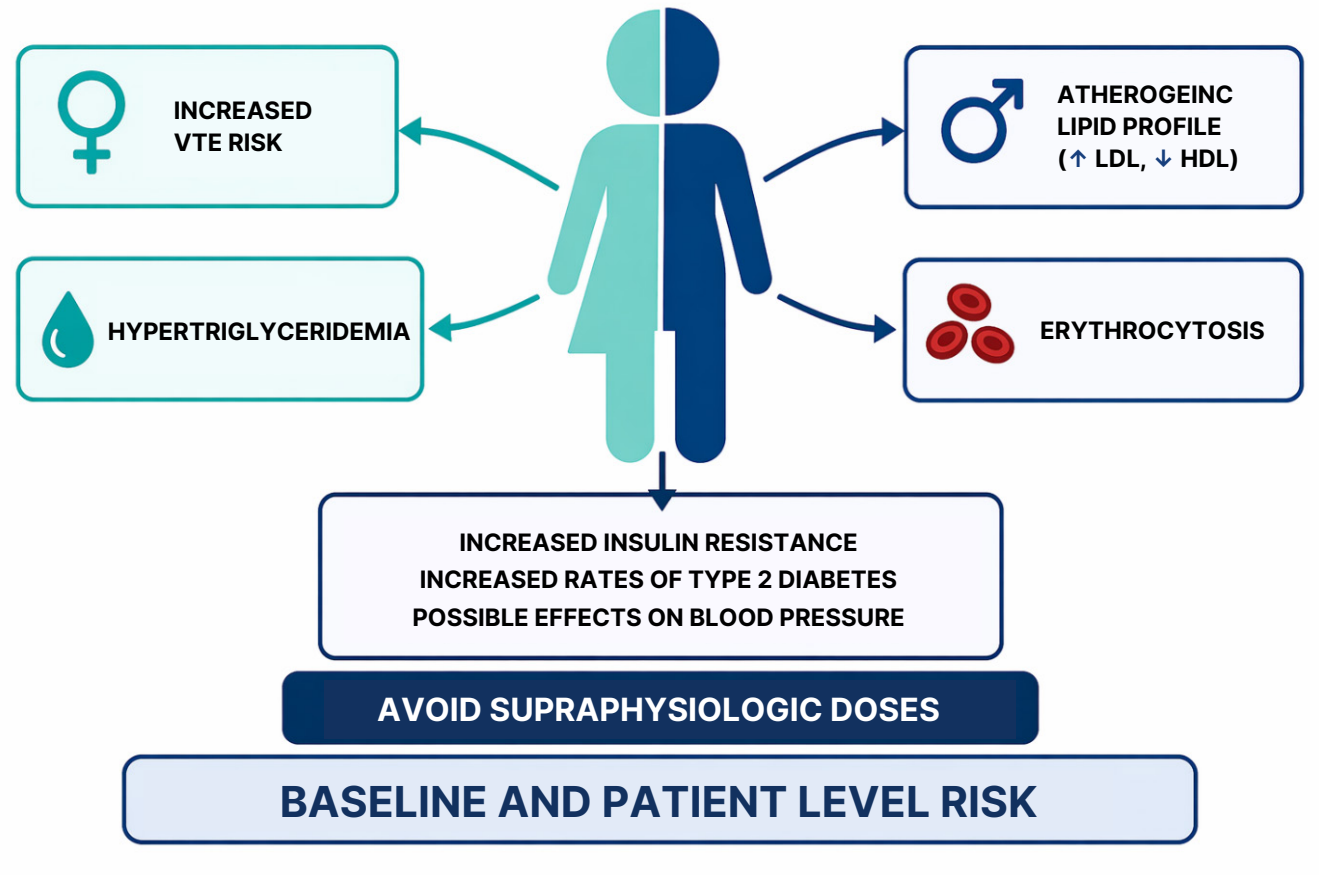

Figure 1. Summary of cardiovascular and venous thromboembolism risks associated with gender-affirming hormone therapy; *courtesy of Irena Druce MD, FRCPC, MSc.*

Abbreviations: HDL: high density lipoprotein; **LDL:** low-density lipoprotein; **VTE:** venous thromboembolism

apply to individuals receiving GAHT remains unknown.[13] In the absence of strong data, the use of progesterone should be individualized, with consideration of potential risks and uncertain benefits.

Beyond hormone-related effects, it is important to recognize that cardiovascular risk in gender-diverse populations is shaped by broader social and structural factors. Transgender individuals experience higher rates of smoking, substance use, and psychosocial stress, as well as reduced access to primary and preventive healthcare. These factors likely contribute substantially to observed differences in cardiovascular outcomes and mortality and may represent a more significant driver of risk than GAHT itself. Accordingly, a comprehensive approach to cardiovascular risk reduction must extend beyond hormone management to include optimization of traditional risk factors and improved access to longitudinal, preventive care.[14,15]

Feminizing GAHT and Venous Thromboembolic Disease

Among the cardiovascular risks associated with GAHT, the most consistent and clinically relevant signal is an increased risk of venous thromboembolism (VTE) in AMAB individuals receiving estrogen therapy. This association is well established and reflects the known prothrombotic effects of systemic estrogen observed in cisgender women.[16]

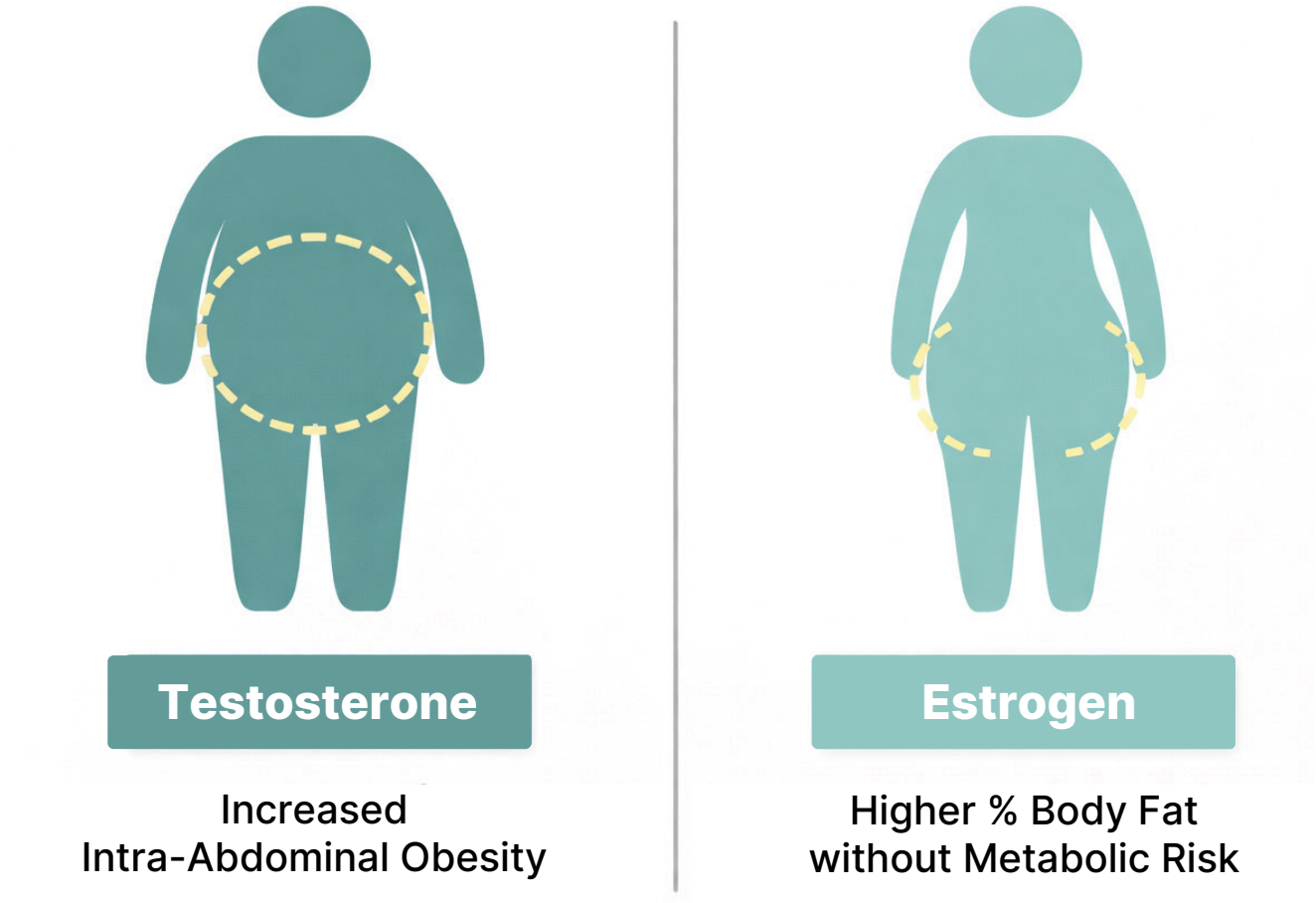

Figure 2. Sex hormone–associated patterns of adipose distribution; *courtesy of Irena Druce MD, FRCPC, MSc.*

Testosterone promotes an android pattern with increased visceral adiposity and higher cardiometabolic risk, whereas estrogen promotes a gynoid pattern with fat deposition in the hips and buttocks, which is typically metabolically less adverse despite higher total body fat.

However, the clinical context differs meaningfully in gender-diverse populations. In cisgender women, estrogen exposure may be time-limited and can often be discontinued if risks outweigh benefits. In contrast, for transgender women, estrogen therapy is a cornerstone of gender-affirming care, with important implications not only for physical characteristics but also for psychological well-being and quality of life. Consequently, discontinuation of estrogen is often not a feasible or appropriate option.[13]

Current practice generally supports the long-term continuation of GAHT, although data on the effects of prolonged estrogen exposure in this population remain limited. Transgender women do not typically undergo an equivalent of menopause, and long-term hormone therapy is commonly maintained. This underscores the importance of risk mitigation rather than treatment avoidance or discontinuation.[13]

In the context of VTE risk, the route of estrogen administration represents one of the few modifiable factors available to clinicians. Oral estrogen undergoes first-pass hepatic metabolism, leading to increased synthesis of clotting factors and a more pronounced prothrombotic effect. In contrast, transdermal estrogen largely bypasses hepatic first-pass metabolism and is associated with a lower impact on coagulation pathways.[17]

While direct comparative data in transgender populations remain limited, evidence from cisgender populations consistently demonstrates a lower risk of venous thromboembolism with transdermal formulations compared to oral estrogen.[18] Accordingly, the route of administration represents a key opportunity for risk reduction in clinical practice. When clinically appropriate, the use of transdermal estrogen should be strongly considered, particularly in individuals with additional risk factors for thrombosis, including increasing age, smoking, obesity, or a personal or family history of VTE.[17,18]

An additional layer of complexity lies in the lack of consensus regarding optimal estradiol targets for individuals receiving feminizing GAHT. In contrast, hormone targets for AFAB individuals on masculinizing therapy can reasonably align with cisgender male reference ranges and remain relatively stable over time. However, cisgender women of reproductive age exhibit wide physiologic variability in estradiol levels across the menstrual cycle, and there is no clear agreement in the literature on which values should be replicated or targeted in feminizing GAHT.[19]

In the context of cardiovascular risk mitigation, particularly VTE, a pragmatic approach is to use the lowest effective estradiol dose that achieves and maintains desired clinical outcomes. This is especially relevant in the maintenance phase, once secondary sexual characteristics have been established, as supraphysiologic exposure is unlikely to confer additional benefit and may increase risk.

In higher-risk individuals, including those with a history of VTE, multidisciplinary management is recommended. Collaboration with thrombosis specialists may help guide decisions regarding the safety of ongoing estrogen therapy, including consideration of anticoagulation when appropriate. Shared decision-making is essential, and should include clear discussion of the potential risks, benefits, and uncertainties surrounding long-term therapy.[17]

Practical Considerations for Cardiovascular Risk Management in Individuals Receiving GAHT

In the absence of robust long-term outcome data, a pragmatic and proactive approach to cardiovascular risk reduction is recommended:

- **Route of estrogen administration:** Prefer transdermal estrogen over oral formulations, particularly in individuals with additional risk factors for VTE, as transdermal preparations are associated with a lower impact on coagulation pathways. Consider injectable formulations where appropriate.
- **Lipid monitoring:** Obtain a baseline lipid profile and monitor it periodically. Consider earlier and more frequent screening, particularly in individuals receiving testosterone or oral estrogen. Include triglyceride measurement where clinically indicated.
- **Glucose metabolism:** Monitor body weight, fasting glucose, and/or HbA1c in individuals with risk factors or features of metabolic syndrome.
- **Blood pressure:** Measure blood pressure routinely and manage according to standard clinical guidelines. Current evidence does not support attributing hypertension solely to GAHT.
- **Weight and body composition:** Monitor weight and body mass index, and counsel patients regarding expected changes in body composition. Support lifestyle interventions where appropriate and pharmacotherapy for obesity as per Canadian guidelines.
- **Hematologic monitoring (testosterone therapy):** Monitor hemoglobin and hematocrit given the risk of erythrocytosis which may predispose to cerebrovascular events. Adjust therapy if levels are above normal cis-male range.

- **Hormone dosing:** Regularly review hormone regimens and ensure that achieved hormone levels remain within physiologic ranges. Supraphysiologic testosterone levels may exacerbate insulin resistance, adverse lipid changes, and erythrocytosis, and should be avoided.
    - For individuals receiving feminizing hormone therapy, maintaining estradiol levels within the physiologic range for premenopausal cisgender women is recommended, while avoiding supraphysiologic levels. In clinical practice, this often corresponds to approximately 200–400 pmol/L, although targets may be individualized based on clinical response and patient-specific goals.
- **VTE risk assessment and mitigation:** Assess individual thrombotic risk factors (e.g., smoking, obesity, personal or family history of VTE) and optimize modifiable risk factors.
- **Multidisciplinary care:** In individuals at higher risk, or those with a history of VTE, collaborate with thrombosis specialists when considering continuation of estrogen therapy, including the potential role of anticoagulation.
- **General preventive care:** Address traditional cardiovascular risk factors, including smoking and substance use, and ensure access to routine primary and preventive care.

Conclusion

At present, limited data directly links GAHT to major cardiovascular outcomes. While hormone-related effects on intermediate risk factors are increasingly recognized, the overall impact of GAHT on cardiovascular disease risk remains uncertain.

At the same time, a growing body of evidence highlights significant disparities in health outcomes and access to care among gender-diverse individuals. The higher rates of cardiovascular morbidity and mortality observed in this population are likely multifactorial, reflecting not only the physiologic effects of hormone therapy but also differences in baseline risk factors, barriers to care, and reduced access to preventive and longitudinal healthcare services.

These findings underscore the importance of a comprehensive approach to cardiovascular risk management in gender-diverse populations. In addition to thoughtful use of GAHT, clinicians should prioritize optimization of traditional risk factors, ensure access to appropriate screening and preventive care, and support ongoing engagement with the healthcare system.

As the evidence base continues to evolve, individualized care, multidisciplinary collaboration, and shared decision-making remain essential. Further research is needed to better define long-term outcomes and to inform strategies that both affirm gender identity and minimize cardiovascular risk.

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